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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,744	09/15/2003	John J. Quinn	1300-0008	6795

23980 7590 01/19/2006

REED INTELLECTUAL PROPERTY LAW GROUP
1400 PAGE MILL ROAD
PALO ALTO, CA 94304-1124

EXAMINER	
WONG, JENNIFER SHIN SHIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,744	QUINN ET AL.	
	Examiner	Art Unit	
	Jennifer Wong	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *September 15, 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *28-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Compy*.

DETAILED ACTION

Election/Restrictions

I. Claims I-27, drawn to methods to detect the presence or absence of a genetic variation by assaying for polymorphisms, classified in class 435, subclass 6.

II. Claims 28-37, drawn to kits to detect polymorphisms, classified in class 536, subclass 23.1.

1. The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the nucleic acids of invention I can be used in a materially different process such as for synthesizing nucleic acids or proteins as well as for diagnostic therapies.

These inventions are distinct for the reasons given above and have acquired a different status in the art as demonstrated by their different classification and recognized divergent subject matter. Further, inventions I and II require different searches that are not coextensive. For instance, the nucleic acids of invention I is not co-extensive with a

patent and non-patent literature search of kits of invention II. Further a finding that invention I is anticipated or obvious over the prior art would not necessarily extend to a finding that the kits of invention II were also anticipated over the prior art. Similarly, a finding that invention I is novel and unobvious over the prior art would not extend to a finding that the kits of invention II are also novel and unobvious over the prior art. Accordingly, examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

2. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is

found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. During a telephone conversation with Karen Canaan on December 28, 2005 a provisional election was made to prosecute the invention of Group I, claims 1-27. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 28-37 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

5. The specification is objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR 1.821(d). In particular, Figure 2 does not include the sequence identifiers for each of the recited sequences. Accordingly, the specification should be amended to include the appropriate SEQ ID NOs for each of the recited sequences.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Beattie et al (U.S. Patent No. 6,268,147).

Beattie teaches methods to detect of sequence variants through the stacking probes, wherein control and variant sequences are PCR amplified with labeled probes,

hybridized to labeled stacking probes which are probes that are allele specific oligonucleotides (ASO) that are designed for a target variant regions, the subsequent hybridization of said labeled amplicon-ASO probe complex with an immobilized ASO on arrays or fluorescent beads designed to "capture," or hybridize to the labeled amplicon-ASO probe complex, and the detection of the labeled amplicon- ASO probe-ASO capture probe complex with arrays or flow cytometry (Figures 1, 13-15). Beattie teaches the application of said method to detect four polymorphisms that cause cystic fibrosis to immobilized ASO capture probes on arrays.

With respect to claim 1, method steps (a) and (b), and claims 6-8 and 12-14, they require the isolation of nucleic acids and PCR amplification with a plurality of primers wherein one set is designed for wild type sequences, and the other set is designed for variant sequences. Beattie teaches "genomic DNA is first extracted from the biological sample...[the] multiplex PCR is first carried out to (using a mixture of PCR primers known to reproducibly amplify a multiplicity of specific genome fragments) to prepare the desired genomic target sequences which contain the known DNA sequence polymorphisms" (column 29, lines 19-26). ASO probes are designed for the polymorphic and control sites (column 11, lines 17-20; column 21, lines 35-37) and "single stranded PCR fragments may be generated by asymmetric PCR, by Streptavin affinity purification when one member of a pair of PCR primers is labeled with biotin" and subsequently, "labeled oligonucleotides, annealing to the target stands immediately adjacent to each polymorphic site, are next mixed with the single-stranded amplified fragments, to introduce the label into the target stands (column 29, lines 34-36 and lines

38-42; claim limitations 12-14). Labeled moieties that can be used to identify and quantify first and second detectable signals include radioactive labels, fluorescent tags, chemiluminescent tags, enzymes that catalyze fluorescent, chemiluminescent or colored compound, biotin, and chemical groups that can be detected by mass or other spectroscopic properties (column 14, lines 11-18) (claim limitations 6-8).

With respect to claim 1, method step (c), Beattie teaches hybridization conditions in which the labeled amplicon-ASO probe are hybridized to an immobilized labeled ASO capture probe and the detection of said complex. Beattie teaches "hybridization is carried out at elevated temperatures or other increased stringency conditions, such at that short capture probe will not by itself form a stable duplex structure with the target sequence. Only if uninterrupted, contiguous base stacking occurs between labeled probe and surface-tethered capture probe...will a strong hybridization signal be seen" (column 8, lines 32-40). Beattie teaches the specific hybridization conditions of the labeled amplicon-ASO probe-ASO capture probe complex and varying temperature conditions (column 22, lines 39-58; column 24, lines 37-48).

With respect to claim 1, method steps (d) and (e) and claim 27, they require detection of the labeled amplicon-labeled probe-immobilized capture probe complex and determining the presence or absence of variant sequences by the relative amounts of control and variant hybridizations. Beattie teaches said hybridization complexes can be detected by autoradiography, microarray analysis, and fluorescence imaging that can detect fluorescence or chemiluminescence such as flow cytometry utilizing

immobilized capture probes on beads (columns 26, lines 65-67; column 19, lines 24-30, column 30, lines 21-30, and column 38, lines 36-47 and Figures 1 and 15). With Beattie's method, the skilled artisan can analyze "simultaneous analysis of numerous known mutations or sequence polymorphism in single genes, a multiplicity of genes, or on a genome-wide scale" (column 19, lines 14-16; claim limitation 27).

With respect to claims 2-4, 15-20, 23-25, Beattie teaches the application of said method to detect cystic fibrosis with immobilized captured probes on arrays. Beattie applies the labeled amplicon-ASO probe-ASO capture probe method to detect cystic fibrosis. Beattie teaches "genomic DNA was isolated from peripheral blood leukocytes from normal individuals and from cystic fibrosis patients" (column 20, lines 6-8) (claim limitations 15). Beattie further teaches "to prepare natural single-stranded target DNA by PCR, primers CF163 and CF164, wherein CF164 was labeled with biotin at the 5' end, was used...to amplify a 138-bp fragment derived from exon 10 in the CFTR gene. This fragment contains four of the most frequent sites of mutations causing cystic fibrosis" (column 20, lines 6-29) (claim limitations 16-20, 23). Beattie further teaches "to prepare DNA by PCR, primer CF164 was labeled with biotin at the 5' end" (column 20, lines 11-20, and lines 22-23). Several target and capture probes for said mutations and its corresponding wild type sequences were designed were radioactively labeled wherein the diagnostic target and capture probes have spacer regions between them as the target and capture probes do not abut one another (column 20, lines 31-66 through column 21, lines 1-37; also illustrated in Figures 1, 13-14) (claim limitations 2-4). Beattie verifies the presence of the mutation ΔF508 in cystic fibrosis patients with this

method compared to those of a normal population, wherein patients are homozygous for said mutation, and the hybridization patterns for the homozygous mutation is higher than the controls, and notes "the hybridization strategy disclosed herein can be used to discriminate between homozygous and heterozygous condition at the ΔF508 site" (column 23, lines 66-67 through column 24, lines 1-32; claim limitation 25).

With respect to claims 5, 9-11, 26, Beattie further teaches that the method of sample-labeled ASO probe-capture probe complex to detect variants can be further applied to microspheres. Beattie teaches "'bead technology' in which different capture probe sequences are tethered to microspheres which are distinguishable by any measurable (detectable) unique physical or chemical property associated with each bead" (column 38, lines 37-40; claim limitation 5). With the hybridization complex "stacking probe must be labeled with a tag that is distinguishable from the spectral property of color-coded beads" and quantitative determination of polymorphisms is done by "the quantity of label associated with each color-coded bead (quantitatively determined using flow cytometry with spectral analysis of individual beads streaming past the detector window) will reveal the allele status at each marker or mutational site analyzed. The stacking probe must be labeled with a tag that is distinguishable from the spectral properties of color-coded beads. If dual labels are used (one used in preannealing with a 'reference' sample and another used in preannealing with a 'test' sample, and the two samples are hybridized together with the mixture of color-coded beads, the relative binding of the two labels (from the stacking probes) to each color-coded beads will reveal the two transcriptional factors simultaneously" (column 39, lines

6-24). Beattie teaches "each polymorphic marker is represented by...a number of allele-specific probes" that are hybridized in tandem with labeled target probes and immobilized capture probes on beads and "the level of each label (from the shorter labeled probes) bound to each color-coded bead will then reveal the allelic status at each polymorphic or mutation-bearing site" and "FlowMetrix" systems are used to measure the levels of fluorescence wherein "different color codes can be distinguished using several fluorescent dyes mixed together at defined ratios at different levels, providing a large number of distinct spectral profiles" (column 40, lines 19-28; Figure 15B, claim limitations 9-11, 26).

With respect to claim 21, Beattie teaches that said method can be used to detect variants including "intronic (noncoding) sequences interspersed within a gene" (column 16, line 36).

With respect to claim 22, Beattie teaches that said method can be used for the "identification of species, strains or individuals through the use of oligonucleotide probes and auxiliary oligonucleotides targeted to nucleotide sequences known to be unique for said species, strains or individuals" (column 19, lines 17-19).

With respect to claim 24, Beattie teaches that this method is applicable to viruses, bacterial and fungi. Beattie teaches "the tandem hybridization method can also be used to unambiguously detect and identify bacterial, viral or other microbial species or strains on the basis of known, unique features of nucleic acid sequences" (column 34, lines 63-67).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Wong whose telephone number is (571) 272-1120. The examiner can normally be reached on Monday-Friday; 8 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer Wong

1/17/06

JEANINE A. GOLDBERG
PRIMARY EXAMINER

1/17/06